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The Patent Office

Cardiff Road
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Gwent NP9 1RH

1. Your reference — PHM 99-098/GB/P

2. Patent application number *(The Patent Office will fill in this part)* — **9921064.3** — 08 SEP 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Zeneca Limited
15 Stanhope Gate
LONDON W1Y 6LN
Great Britain

THE PATENT OFFICE
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- 8 SEP 1999
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Patents ADP number *(if you know it)* — 6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — DRUG COMBINATION

5. Name of your agent *(if you have one)* — DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Global Intellectual Property, Patents
AstraZeneca PLC
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG
Great Britain

Patents ADP number *(if you know it)* — 1030618002

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a) any applicant named in part 3 is not an inventor, or

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See note (b))

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DRUG COMBINATION

The invention relates to the use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in combination with a fibrate drug, the use of such a combination in treating hyperlipidaemia in mammals, and medicaments containing such a combination for use in such treatments.

Hypercholesterolaemia is one of the strongest risk factors for atherosclerosis which is associated with coronary artery disease (including angina pectoris, myocardial infarction and mortality), stroke (including cerebro vascular accident and transient ischaemic attack) and peripheral arterial occlusive disease. Several types of hypercholesterolaemia exist. The magnitude of hypercholesterolaemia may have consequences for the therapy, but in general, any reduction of elevated plasma cholesterol levels is generally accepted to result in an improvement of the risk profile. Guidelines exist for the treatment of hypercholesterolaemia, American Heart Association (AHA) (Anon 1988), Updated Sheffield treatment tables (Heart (1998) 80 Supp.2 S1-S29) and Recommendations of the task force of the European Society of Cardiology Guidelines (Pyorala 1994). Dietary improvement and increased exercise is an essential first step and should be maintained even if drug therapy is instituted, but the therapeutic potential of drug therapy is significantly larger. Several types of drug therapy for hypercholesterolaemia are currently available.

Fibrate drugs are members of the fibric acid group of hypolipidiaemic agents the mechanisms of which are not well understood but are thought to act through activating lipoprotein lipase to induce lipolysis and decreased fatty acid flux through the liver and so reduce VLDL synthesis. Fibrates also alter LDL metabolism by stimulating receptor activity. It is believed they act through the peroxisomal proliferating activator receptor-α (PPAR-α) and affect gene activation at a number of genes involved in atheroma. The major effect of fibrates is to reduce triglycerides (or VLDL); the effect on LDL is more complex - they can cause modest reductions in LDL in patients with high LDL and raising LDL in patients with low LDL and high TG, and possible further effects may be attributable to improved insulin sensitivity. Examples of fibrate drugs include, bezafibrate, ciprofibrate, fenofibrate and gemfibrozol.

HMG-CoA reductase inhibitors are the most widely used prescription medication for the treatment of hypercholesterolaemia. By inhibiting the rate-controlling step in cholesterol biosynthesis, these agents effectively lower the plasma concentrations of atherogenic particles containing cholesterol such as low-density lipoprotein (LDL-C) and very low-density lipoprotein (VLDL-C). Partial inhibition of hepatic cholesterol synthesis causes up-regulation of hepatic membrane LDL-C receptors which are responsible for the clearance of LDL-C from the circulation. In addition, reduced hepatic synthesis of cholesterol is thought to result in a modest reduction in the secretion of VLDL-C particles by the liver. Clinical trials such as the Scandinavian Simvastatin Survival Study, of certain HMG Co A-reductase inhibitors confirm that reductions in cardiovascular morbidity and mortality, and regression of atherosclerotic vascular lesions, may be achieved. Various HMG Co A-reductase inhibitors are marketed, and are collectively referred to as 'statins'.

Despite the impressive benefits of statin therapy, less than optimal therapeutic results may be achieved in some subjects, particularly in the more severe classes of hypercholesterolaemia. This can be due to the occurrence of reversible increases in liver transaminase levels at higher dose levels of statins as well as differences in efficacy between different statins. Clinically important (>3 times upper limit of normal [ULN]) elevations in serum alanine aminotransferase (ALT) have been reported for atorvastatin in 0.8 per cent at low doses of atorvastatin higher frequencies are observed at higher doses (European Summary of Product Characteristics [SmPC] for atorvastatin [Lipitor™]). In all cases the effect is dose-related and reversible. In general it is the incidence of raised ALT which limits dose escalation of statins rather than the absence of a further possible increase in efficacy.

The first generation statins (such as lovastatin, pravastatin and simvastatin - prodrug derivatives of fungal metabolites - and fluvastatin) are categorised in that they achieve only a limited cholesterol lowering affect, with their dose administered being limited by elevations in serum ALT. Second generation "super statins" (such as atorvastatin - synthetic compounds-structurally distinct from first generation compounds) inhibitors are categorised in that they lower cholesterol levels to a much higher degree than the earlier first generation of statins before their dose is limited by serum ALT levels. Atorvastatin has been successful over the first generation of statins. Since its launch in the USA atorvastatin has reached sales in 1998, doubling from 1997, of $2.2 billion, capturing 38% of new prescriptions for cholesterol-

lowering agents in the US now the most widely prescribed hypolipidaemic agent in the US (Warner-Lambert 1998 annual results).

An additional adverse event which is found with the use of statins is myopathy, defined as symptoms of muscle pain, tenderness and weakness, with creatinine kinase (CK) values >10 x Upper Limit of Normal (ULN). This adverse event is not considered dose related, and in addition the adverse events are potentially more serious, and consequently is more problematical, especially in patients receiving concomitant drugs, as discussed below. In severe cases this can lead to rhabdomyolysis, which is a rare life threatening condition sometimes also associated with renal failure. The incidence of raised CK levels (>3x ULN) for statins has been reported as 3.1 per cent. (SmPC for atorvastatin), where >10x ULN on two separate occasions at least 1 week apart, is a clinically significant level = myositis. Myopathy and rhabdomyolysis have been associated with taking a statin in combination with gemfibrozil, niacin, cyclosporin or erythromycin, (HMG CoA reductase inhibitors, Hunninghake, Current Opinion in Lipidology (1992) 3, 22-28) which are all substrates for P450 3A4. Additionally, adverse events associated with taking a fibrate drug have also been reported to increase with concomitant statin therapy, such as a myosistis-flu like syndrome which occasionally occurs in patients receiving gemfibrozil, increases to 5% of patients when a statin is also administered. The increase in adverse events associated with taking a combination of a statin drug with one of the other drugs mentioned above is probably due to drug:drug interaction related to the metabolism of most statins by cytochrome P450 3A4. Therefore when a drug which is also metabolised by P450 3A4 is administered alongside a statin, interactions are more likely to occur, such as muscle damage which are possibly due to elevated statin levels in muscle cells inhibiting farnesylation and geranylgeranylation of muscle proteins. Therefore, currently on the labels of all commercially available statins combination therapy with other drugs metabolised by P450 3A4 is not recommended and is contraindicated in certain cases.

Nearly all drugs are metabolised to some degree in the human, generally to a less lipid soluble compound which is more easily excreted by the kidney. Many of the drug metabolic enzymes are found in the endoplasmic reticulum (which form microsomes upon homogenisation) of hepatocytes. The liver is the major site of drug metabolism because the

liver cells (hepatocytes) contain particularly high concentrations of drug metabolising enzymes. Cytochrome P450 is a family of isoenzymes found in hepatic microsomes. Six specific P450 isoenzymes are responsible for the metabolism of most of the commonly used drugs, namely P450 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

A major disadvantage of the currently available "superstatin" , atorvastatin, is that atorvastatin is metabolised by cytochrome P450 enzymes in particular 3A4, which may cause drug interactions with other drugs which are inducers, inhibitors or substrates of the same P450 enzyme which metabolises atorvastatin. All of the first generation of statins are metabolised by P450 also. However, the rate of metabolism of pravastatin is sufficiently low that it is less clinically relevant to potential drug interactions.

(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the calcium salt of which is disclosed in Figure 1 below) hereinafter referred to as the Agent is also a statin and belongs to the class of what is now called in the literature a "superstatin".

The Agent is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of HMG-CoA reductase. The Agent is taught as useful in the treatment of hypercholesterolaemia, hyperlipoproteinaemia and atherosclerosis.

The Agent is not metabolised to any significant extent by any cytochrome P450, in particular 3A4, and therefore does not possess the same potential for drug interactions shared with the currently available "superstatin", i.e. atorvastatin, or the other currently available statins.

Combination of a statin with a fibrate drug is contraindicated on the labels, both in the USA and Europe, of all commercially available statins. Despite the possibility of the occurrence of serious drug interactions doctors do prescribe combination therapy of a statin and a fibrate drug to patients with more severe levels of hypercholesterolaemia, such as in patients with familial combined hyperlipidaemia, where the risk of a serious drug interaction is outweighed by the benefits of the combination therapy. It is recommended that where combination therapy of a fibrate drug and a statin is prescribed that patients should have their CK value determined on a regular basis, typically every 6-weeks, until a stable pattern is

established. Therapy is stopped if muscle symptoms occur in association with elevated CK activity. However, as quoted from the US label of Lipitor™ "there is no assurance that such monitoring [of CK levels] will prevent the occurrence of severe myopathy".

We have discovered that the Agent is extremely effective at treating mixed hyperlipidemia and hypertriglyceridemia in patients when combined with a fibrate drug and that the Agent is not metabolised by cytochrome P450 enzymes. Therefore we have found through the use of the Agent in a clinical study that the Agent may be conveniently dosed to patients who are also taking a fibrate drug without any clinically significant side effects associated with the concomitant dosing of the Agent and the fibrate drug. In addition much higher levels of lipid lowering than has previously been achieved can be achieved by the use of the Agent and a fibrate drug. The combination is of most use in mixed hyperlipidemia where the LDL and VLDL/TGs are both elevated.

We present as the first feature of the invention a method of providing safe non-interacting lipid lowering combination therapy to a mammal, including a human patient, preferably a patient suffering mixed hyperlipidemia and hypertriglyceridemia, which method comprises administering to the patient the Agent and a fibrate drug.

By the term "combination" as used herein we mean either (1) that the Agent and the fibrate drug of the combination are administered together in the same pharmaceutical formulation or (2) that the Agent and the drug are administered separately. When administered separately components of the combination may be administered to the patient simultaneously or sequentially.

By the term "fibrate drug" we mean the class of drugs which are based around the structure/activity of fibric acid and such drugs include the following commercially available versions; bezafibrate, clofibrate, ciprofibrate, fenofibrate and gemfibrizol, preferably fenofibrate.

Preferred patients in which the combination of the invention is to be administered are those who have already been found to suffer from myopathy or rhabdomylosis when treated with a statin and/or a fibrate drug which is metabolised by P450 3A4.

Particular patients who may benefit from the method of the invention are those who:

1) suffer combined (type IIb) hypercholesterolaemia (typically LDL-C≥ 135 mg/dL and TG≥200 mg/dL);

2) suffer familial (type IV and V) hypercholesterolaemia;

3) patients suffering secondary hypercholesterolaemia from such conditions as:

a) diabetes (type I or II),

b) nephrotic syndrome,

c) uremia,

d) hyperthyroidism, and

e) obstructive liver disease.

4) patients with established CHD or other atherosclerotic disease, such a PVD, stroke or peripheral arterial occlusive disease;

5) patients who are at high risk of developing CHD or other atherosclerotic disease, such as described above, because of a combination of risk factors. The term "high risk" is defined in the "Recommendations of Second Joint Task Force of European and other Societies on Coronary Prevention"; (Wood, D. et. al. European Heart Journal, Atherosclerosis and Journal of Hypertension 1998) as absolute CHD risk of ≥ 20% over 10 years or will exceed 20% if projected to age 60 years. Whether a patient is at high risk or not may be determined by the charts which accompany the above recommendations and which charts are incorporated herein by reference. For example a male patient in his 40s who smokes and has a systolic blood pressure of 180 mm Hg or higher and a total plasma cholesterol concentration of 7 mmol/L or higher will be classified as high risk. Similarly other guidelines for reducing risk factors may be applied such as those described in;

a) JAMA, June 16, 1993-Vol 629, No.23, Pages 3015-3023 - "Summary of the NCEP Adult Treatment Panel II Report - specifically Figure 1. Page 3018-3019 which is incorporated herein by reference.

b) Post Graduate Medical Journal 1993; 69(811): 359-369 - "Management of hyperlipidaemia: guidelines of the British Hyperlipidaemic Association"- specifically Table V and Table VI are incorporated herein by reference.

c) Heart 1998; 80 Supplement 2:S1-S29 - "Joint British recommendations on prevention of coronary heart disease in clinical practice" - specifically Figure 1 on pages S4-S5.

d) The Lancet 1995; December 2, Vol.346, 1467-1471 - "Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart disease" - specifically the Table appearing at page 1468 is incorporated herein by reference.

6) patients who are about to or have already undertaken a heart transplant;

The statin therapy may be administered so as to achieve in the patient receiving a fibrate drug:

1) a reduction of LDL-C of at least 30, 40, 50, 60, 70 or 80%.

2) a maintenance or increase of HDL-C of at least 5, 10, 15%.

3) a reduction in triglycerides of at least 10, 20, 30 or 40%.

The combination of the fibrate and the Agent may be applied as separate dosage forms, which may be taken simultaneously or sequentially, or in a combined dosage form.

Doses of the Agent which are administered are at the discretion of the attendant physician generally taking into account the severity of the disease, the age, weight and sex of the patient. However typical doses will be from 5 to 80 mg per day orally, preferably as a once a day oral tablet form.

Other features of the invention include the use of 5-80mg of the Agent in combinations described hereinabove. When a dose range of 5 to 80 mg per day is referred to herein for the Agent other particular dosage ranges which are further independent aspects of the invention include (as appropriate) 10 to 80 mg per day, 10 to 60 mg per day, 10 to 40 mg per day, 5 to 40 mg per day, 5 to 20 mg per day, 10 to 20 mg per day, 20 to 60 mg per day, 20 to 40 mg per day and 40 to 60 mg per day. Particular dosages are 5, 10, 20, 40 and 80mg per day. A particularly suitable starting dose of the Agent in the methods referred herein is 5 to 10 mg per day, especially 10 mg per day.

Doses of the fibrate drug which are administered in the combination of the invention also are at the discretion of the attendant physician taking into account all of the above factors

plus in particular which fibrate drug is used.

For clofibrate (such as Atromid-S®) 20-30 mg/kg body weight daily in 2 or 3 divided oral doses after meals is typical.

For bezofibrate (such as Bezalip®) 400 mg once a day orally, after food at night or in the morning, is typical.

For fenofibrate (such as Lipantil®) 200 mg once a day, or 62 mg three times a day, with food is typical.

For gemfibrozil (such as Lopid®) 600 mg twice a day orally is typical.

For cipofibrate (such as Modalim®) 100 mg once a day orally is typical.

A preferred fibrate drug is fenofibrate.

ABBREVIATIONS AND CONVENTIONS

Abbreviation	Term
ALT	alanine aminotransferase
ALP	alkaline phosphatase
apo B	apolipoprotein B 100
AST	aspartate aminotransferase
AUC	area under the concentration curve from zero to infinity
AUC(0-t)	area under the curve of plasma concentration against time from zero to time of last quantifiable concentration
C_{max}	maximum concentration
CK	creatinine kinase
ECG	electrocardiogram
EDTA	ethylenediamine-tetraacetic acid
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPLC	high-performance liquid chromatography

Abbreviation	Term
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
MVA	mevalonic acid
NC	not calculable
THC	tetrahydrocannabinol
TG	triglyceride
$t_{½}$	terminal elimination half-life
t_{max}	time of maximum concentration

The invention is illustrated by the following non-limiting examples:

Clinical Trial

A Randomised, Non-controlled, Single-centre, Open-label, 3-way Crossover Trial to Assess the Effect of Co-administration of the Agent and Fenofibrate on the Pharmacokinetics of Each Compound in Healthy Male Volunteers

Objectives: The primary objective of this trial is to assess the effect of co-administration of the Agent and fenofibrate on the pharmacokinetics of both the Agent and fenofibrate

The safety of all volunteers will be ensured by clinical monitoring

Type and number of volunteers: 14 healthy male volunteers

Trial design: The trial will be a randomised, non-controlled, 3-way crossover study carried out at a single centre

Trial treatment: This trial will consist of three 7-day treatment periods (Periods A, B,

and C). Volunteers will receive, in random order, a 10 mg capsule of the Agentonce daily for 7 days, a 67 mg fenofibrate capsule 3 times daily for 7 days and the combination for 7 days.

There will be a minimum of a 3-week washout between each trial period

Duration of treatment: The study will consist of 3 periods of 7-day dosing (a total of 21 dosing days) with a 3-week washout between dosing in Periods A, B and C

Primary endpoints: The primary endpoints are:

- AUC(0-24) and C_{max} of the Agent in the presence and absence of fenofibrate
- AUC(0-8) and C_{max} of fenofibrate in the presence and absence of the Agent

Secondary endpoints: the secondary endpoints are:

- t_{max}, $t_{1/2}$, C_{min} for the Agent in the presence and absence of fenofibrate
- t_{max}, $t_{1/2}$, C_{min} for fenofibrate in the presence and absence of the Agent
- safety assessments: symptoms, blood pressure and pulse rate, ECG, clinical chemistry, haematology and urinalysis

TRIAL PLAN

Summary of procedures - overall plan for Trial Periods A, B and C

Trial Days	Medical	Doses of the Agent / fenofibrate or combination	P & BP	12 lead ECG	Safety Blood & Urine	Kinetics of the Agent	Kinetics Fenofibrate

Pre-trial	+		+	+	+[a]		
-1					+[b]		
1		+				+[c]	+[c]
2		+			+[b]	+[d]	+[e]
3		+				+[d]	+[e]
4		+			+[b]		
5		+					
6		+			+[b]	+[d]	+[e]
7		+	+	+		+[d]	+[e]
8					+[b]	+[d]	
9						+[d]	
10					+[b]	+[d]	
Post-trial	+		+	+	+[a]	+[d]	

[a]Full clinical chemistry, haematology and urine labstix.

[b]Clinical chemistry only: urea, creatinine, total protein, albumin, uric acid, total bilirubin (and unconjugated and conjugated bilirubin if total bilirubin raised), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotranseferase (AST), gamma glutamyltransferase, creatine kinase (CK), sodium, potassium, calcium, cholesterol and triglycerides.

[c] Pre-dose all trial periods.

[d]Only trial periods when volunteers receive the Agent

eonly trial periods when volunteers receive fenofibrate

P = pulse; BP = blood pressure

TRIAL PLAN II

Trial Day 7 in Periods A, B and C

Time	P & BP (L)	12 lead ECG	Safety blood & urine [e]	Kinetics of the Agent [b]	Kinetics fenofibrate[c]	Meals & Fluids
Pre-dose	+	+		+	+	B
Dose (0 h)						D
0.5 h				+	+	
1 h				+	+	

2 h				+	+	D
3 h	+	+		+	+	
4 h				+	+	M, F
5 h	+	+		+	+	
6 h				+	+	
8 h				+	+	S
10 h				+		M
12 h	+	+		+		F
14 h						S
18 h				+		W
24 h	+	+	+[a]	+		
30 h				+		
48 h				+		
54 h				+		
72 h			+[a]	+		

[a]clinical chemistry only: urea, creatinine, total protein, albumin, uric acid, total bilirubin (and unconjugated and conjugated bilirubin if total bilirubin raised), alkaline phosphatase, ALT, AST, gamma glutamyltransferase, CK, sodium, potassium, calcium, cholesterol and triglycerides.

[b]Only trial periods when volunteers receive the Agent.

[c]Only trial periods when volunteers receive fenofibrate

L = lying; P = pulse; BP = blood pressure; D = drink; S = snack; M = meal; F = free access to permitted fluid and food; W = free access to water only

1 OBJECTIVES

1.1 Primary objective

The primary objective of this trial is to assess the effect of co-administration of the Agent and fenofibrate on the pharmacokinetics of both the Agent and fenofibrate.

1.2 Secondary objective

There is no secondary objective for this trial.

The safety of all volunteers will be ensured by clinical monitoring.

1.3 Design

The trial will be a randomised, non-controlled, open-label, 3-way crossover study carried out at a single centre.

Volunteers will receive 3 treatment regimens in random order:

- 10 mg of the Agent once daily for 7 days
- fenofibrate (Lipantil™) 67 mg x 3 daily for 7 days
- the Agent (10 mg once daily) and fenofibrate (Lipantil™, 67 mg x 3 daily) given in combination for 7 days

There will be a minimum of 3 weeks (21 days) washout between each treatment period.

1.4 Inclusion criteria

For inclusion in the trial, volunteers must meet all of the following criteria:

- male, aged between 18 and 65 years inclusive
- normal clinical examination, including medical history, resting electrocardiogram (ECG) and 24-hour continuous ambulatory ECG (if not performed in the past 12 months)
- negative screens for serum hepatitis B surface antigen and hepatitis C antibody and a normal screen for ferritin within the previous 12 months
- weight not differing by more than 20% from the desirable weight (Metropolitan Height and Weight Tables)
- written informed consent obtained

1.5 Exclusion criteria

Volunteers must be excluded from the trial if any of the following criteria are met:

- use of any medication or therapy, including drugs of abuse

- receipt of another new chemical entity in the 4 months before dosing in this trial (a new chemical entity is defined as a compound which has not been submitted for marketing authorisation)
- participation in another trial within 3 months before the start of the present trial, apart from non-invasive methodology trials in which no drugs were given
- any acute illness within 2 weeks before the start of the trial
- any clinically significant abnormalities in clinical chemistry, haematology or urinalysis results. In addition the following clinical chemistry parameters should be no greater than the upper limit of normal: total bilirubin, ALT, AST and CK
- risk (in the investigator's opinion) of transmitting, through blood or other body fluids, the agents responsible for acquired immune deficiency syndrome (AIDS), hepatitis B or hepatitis C
- definite or suspected personal history or family history of adverse drug reactions, or hypersensitivity to drugs with a similar chemical structure to the Agent or related statins, or fenofibrate and related fibrate drugs
- history or presence of gastrointestinal, hepatic, biliary or renal disease or other condition known to interfere with absorption, distribution, metabolism or excretion of drugs
- history of Gilbert's syndrome
- if participation in the trial would result in the volunteer donating more than 1350 ml of blood in the 12 months before the end of the trial
- excessive intake of alcohol, defined as a maximum weekly intake of greater than 28 units (1 unit equals half a pint of beer or a measure of spirits)
- treatment in the previous 3 months with any drug known to have a well-defined potential for hepatotoxicity (eg, halothane)
- clinical judgement by the investigator or the volunteer's general practitioner that the volunteer should not participate in the trial

1.6 Volunteer restrictions

Volunteers will be required to:

- abstain from taking any medication (including over-the-counter remedies) from 96 hours before Trial Day 1 to 72 hours after receiving the last dose of the Agent or morning dose of fenofibrate in each trial period unless the investigator has given prior consent
- fast from midnight on the night before each trial day and eat a light breakfast on arrival on Trial Day 1 to 7 in each trial period
- refrain from driving, cycling, using machinery (drills, sanders, sharp instruments etc.) for 24 hours after receiving first dose on Trial Day 7 in each period
- remain for 24 hours after receiving first dose on Trial Day 7 in each trial period
- abstain from smoking, consuming grapefruit, grapefruit juice, liquorice or caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate and cola) from midnight before Trial Day 1 until 72 hours after receiving the last dose of the Agent or morning dose of fenofibrate in each trial period
- abstain from drinking alcohol from 96 hours before Trial Day 1 until 72 hours after receiving the last dose of the Agent or morning dose fenofibrate in each trial period
- refrain from physical exercise from 96 hours before Trial Day 1 until 72 hours after receiving the last of the Agent or morning dose of fenofibrate in each trial period
- refrain from potentially hazardous work or activities, from receiving the first dose of the Agent or fenofibrate until the post-trial medical
- abstain from donating blood during the trial and for 3 months following their last dose of trial treatment

1.7 Formulation, presentation and storage

1.7.1 Dosage and administration

Capsules of the Agent or fenofibrate will be taken orally with 200 ml of purified water with the volunteer sitting in an upright position.

On Trial Days 1 to 7 of each treatment period, volunteers will receive one of the following treatments:

- 1 x 10 mg capsule of the Agent to be taken between 08:30 and 09:30 hours
- 3 x 67 mg fenofibrate capsules
  - the 1st capsule to be taken between 08:30 and 09:30 hours
  - the 2nd capsule to be taken between 16:30 and 17:30 hours with food
  - the 3rd capsule to be taken between 22:30 and 23:30 hours with food
- 1 x 10 mg ZD4522 capsule and 3 x 67 mg fenofibrate capsules:
  - 1 ZD4522 capsule and the 1st fenofibrate capsule to be taken simultaneously between 08:30 and 09:30 hours
  - the 2nd fenofibrate capsule to be taken between 16:30 and 17:30 hours with food
  - the 3rd fenofibrate capsule to be taken between 22:30 and 23:30 hours with food

On Trial Days 1 to 6 of each trial period, volunteers will visit the unit daily and will be allowed to leave the unit immediately after administration of doses of the Agent, fenofibrate or the the Agent / fenofibrate combination, except on Trial Day 7 when volunteers will remain resident for 24 hours.

In trial periods when the volunteers are randomised to fenofibrate, they will take the further 2 doses of fenofibrate at home. The volunteers will be provided with 1 pot of fenofibrate to be taken as outlined above. Volunteers will be issued with a pre-set timer to ensure that the dose is taken at the correct time, and a diary card to document the dose was taken.

When the the Agent and fenofibrate are given to the volunteers, the tear-off labels will be attached to the appropriate case report form (CRF). The investigator must ensure that each volunteer receives the correct treatment.

1.8 Clinical and laboratory assessments

1.8.1 Primary endpoints

The following parameters will be measured as primary endpoints:

- AUC(0-24) and C_{max} of the Agent in the presence and absence of fenofibrate
- AUC(0-8) and C_{max} of fenofibrate in the presence and absence of the Agent

1.8.2 Secondary endpoints

The following parameters will be measured as secondary endpoints:

- t_{max}, $t_{1/2}$, C_{min} for the Agent in the presence and absence of fenofibrate
- t_{max}, $t_{1/2}$ and C_{min} for fenofibrate in the presence and absence of the Agent

safety assessments: symptoms, blood pressure and pulse rate, ECG, clinical chemistry, haematology and urinalysis

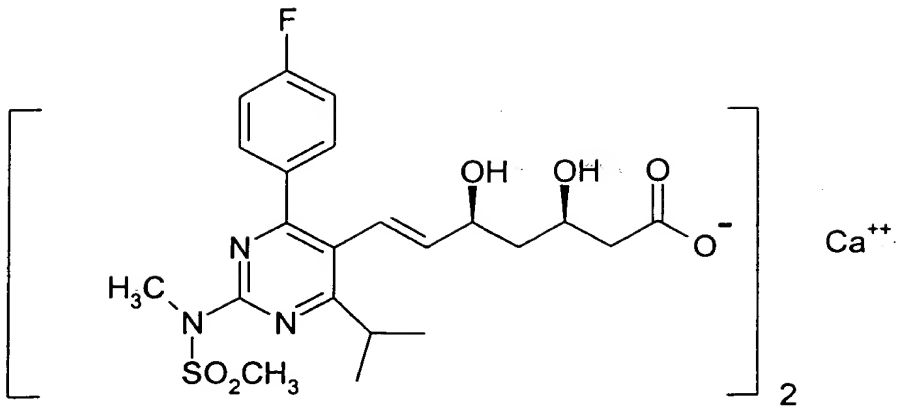

Fig.1